to "array" in claims 1, 11, 12 and 18. Support for this amendment can be found in originally filed claims 1, 11, 12 and 18. Claim 9 has been amended to correct an inadvertent grammatical error. Applicant submits that these amendments are fully supported by the specification and that no new matter has been added.

Information Disclosure Statement

Applicant respectfully requests that a copy of the 1449 Form, listing all documents that were submitted with the Information Disclosure Statement filed on February 14, 2000, marked as being considered and initialed by the Examiner, be returned with the next official communication.

§112 Rejection of the Claims

Claims 1-18 were rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter that allegedly was not described or enabled in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The Examiner has indicated that language "wherein each n-mer is at least 8 nucleotides in length" is not supported by the specification because no upper limit is specified. Language relating to "wherein each n-mer is at least 8 nucleotides in length" has been deleted from the claims. The Examiner has also indicated that language relating to a "microarray" is not supported by the specification. Language relating to "microarrays" has been deleted from the claims. Accordingly, these rejections under 35 U.S.C. § 112, first paragraph, are rendered moot. Withdrawal of these written description and enablement rejections under 35 U.S.C. § 112, first paragraph, is respectfully requested.

§103 Rejection of the Claims

Claims 1-18 were rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Cantor et al. (U.S. Patent No. 5,631,134, filed June 5, 1995) in view of Southern (U.S.Patent No. 5,700,637, filed April 19, 1994), Yershov et al. (Proc. Natl. Acad. Sci., USA, 93: 4913-4918 (1993)) and Fodor et al. (U.S. Patent No. 5,800,992). According to the Examiner, the '134 patent

teaches the claimed subject matter of the present application.

The claims are directed to hybridization methods for determining the presence of a mutation in a target polynucleotide or for determining whether two or more target polynucleotides are identical without sequencing the target polynucleotides, wherein these methods have a false positive rate of less than 1 per 3900 bp. None of the cited references discloses or teaches methods that can detect nucleic acids with such a low false positive rate. Therefore, the cited references do not teach or suggest all of the claim limitations as required for obviousness.

In particular, claim 1 is directed to a method of determining the presence of a mutation in a target polynucleotide without sequencing the target polynucleotide, wherein the method has a false positive rate of less than 1 per 3900 bp. The steps recited in claim 1 include (a) providing at least two identical polynucleotide probe arrays, wherein each probe comprises a double stranded region and a single-stranded n-mer overhang region such that the overhangs in each array constitute a complete set of n-mers; (b) hybridizing the target polynucleotide to said overhangs of probe polynucleotides in one array to generate a target hybridization pattern; (c) hybridizing a reference polynucleotide to said overhangs of probe polynucleotides in a second array to generate a reference hybridization pattern; and (d) determining the presence of a mutation in the target polynucleotide by comparing the reference and target hybridization patterns.

Claim 12 is directed to a method of determining whether two or more target polynucleotides are identical, wherein the method has a false positive rate of less than 1 per 3900 bp. Step (a) of claim 12 is the same as step (a) of claim 1. Step (b) of claim 12 involves hybridizing first target polynucleotide to the overhangs of probe polynucleotides in one array to generate a first hybridization pattern. Step (c) of claim 12 involves hybridizing second target polynucleotide to the overhangs of probe polynucleotides in a second array to generate a second hybridization pattern. Step (d) of claim 12 involves comparing the first and second hybridization patterns.

The test for obviousness under § 103 must take into consideration the invention as a whole; that is, one must consider the particular problem solved by the combination of elements

that define the invention. *Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 1143, 227 U.S.P.Q. 543, 551 (Fed. Cir. 1985). The Examiner must also recognize and consider not only the similarities but also the critical differences between the claimed invention and the prior art. *In re Bond*, 910 F.2d 831, 834, 15 U.S.P.Q.2d (BNA) 1566, 1568 (Fed. Cir. 1990), *reh'g denied*, 1990 U.S. App. LEXIS 19971 (Fed. Cir. 1990). Hindsight must also be avoided. *Id.* The Examiner cannot use the Appellant's structure as a "template" and simply select elements from the references to reconstruct the claimed invention. *In re Gorman,* 933 F.2d 982, 987, 18 U.S.P.Q.2d (BNA) 1885, 1888 (Fed. Cir. 1991).

Applicant respectfully submits that the present claims are not obvious over the cited combination of references. For example, none of the references provides a teaching of a hybridization method that provides sequence information with a false positive rate of less than 1 per 3900 bp.

Cantor et al. (U.S. Patent 5,631,134) describes the problems facing sequencing by hybridization including poor levels of discrimination, sequence ambiguities and the like. *See* col. 2, line 37 to col. 3, line 21. However, Cantor et al. provide no teaching that such methods can be performed with a false positive rate lower than 1 per 3900 bp. For example, Cantor et al. teach a method for unambiguously revealing 12 out of 16 possible sequences at col. 16, lines 40-61. However, the remaining (four) sequences would be divided into two ambiguous pairs each. Such a rate (25%) of false positives or of ambiguities is much higher than the rate provided by the present invention.

Similarly, Southern (U.S. Patent 5,700,637) describes problems associated with determining a nucleic acid sequence by hybridization and even illustrates how very difficult it can be to distinguish a positive from a negative hybridization event. *See, e.g.*, Figures 3 and 4. However, Southern teaches ranking the possible sequences by number of occurrences (times detected), where the correct sequence is only one of a number of possibilities; Southern also admits that the exhaustive method described therein could not be used on sequences comprising all four bases (only two sequences containing just deoxycytidine and deoxythymidine nucleotides were tested). *See* Page 1013, right column, last paragraph. No discussion on the rate of detecting false positives is provided. However, Southern does provide a statistical analysis of a set of

ranked potential sequences, showing that in some cases the RSS (sum of squares of residuals) is very close for the correct sequence ranked number 1 (e.g., 0.388) and a mismatched sequence ranked number 2 (0.393). Sequence assignments based on such close statistical rankings would not provide one of skill in the art with an understanding that the Southern method had a false positive rate lower than 1 per 3900 bp.

Yershov et al. (Proc. Natl. Acad. Sci., USA, 93: 4913-4918 (1993)) also provides no teaching on a method that can be performed with a false positive rate lower than 1 per 3900 bp. Instead, Yershov et al. merely illustrate hybridization of defined targets to small numbers (e.g., 2-6) of "gel elements" that each contain a distinct immobilized probe. In one experiment, terminal and penultimate sequence mismatches, and a rather stable G-T mismatch, were observed that might have lead to confusing results if the hybridizing sequence was not already known (only an approximate two-fold difference in signal intensity was observed). *See* Fig. 2 and Page 4916, Left Col., Fourth Complete Paragraph. Accordingly, Yershov et al. does provide a teaching of a method that has a false positive rate lower than 1 per 3900 bp.

Fodor et al. (U.S. Patent No. 5,800,992) describes certain complications arising from detection and analysis of nucleic acid hybridization to probe arrays at Page 23, Line 28 to Page 25, Line 37. However, Fodor et al. also does not disclose or describe that the method can be performed with a false positive rate lower than 1 per 3900 bp.

Accordingly, the combination of Cantor et al. (U.S. Patent No. 5,631,134) in view of Southern (U.S. Patent No. 5,700,637), Yershov et al. (Proc. Natl. Acad. Sci., USA, 93: 4913-4918 (1993)) and Fodor et al. (U.S. Patent No. 5,800,992) does not disclose or teach the subject matter of claims 1-18. Applicant respectfully requests withdrawal of this rejection under 35 U.S.C. § 103(a).

Conclusion

Applicant respectfully submits that the claims are in condition for allowance and notification to that effect is earnestly requested. The Examiner is invited to telephone Applicant's attorney (516) 795-6820 to facilitate prosecution of this application.

If necessary, please charge any additional fees or credit overpayment to Deposit Account No. 19-0743.

Respectfully submitted,

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CERTIFICATE UNDER 37 CFR 1.8: The undersigned hereby certifies that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail, in an envelope addressed to: Box AF, Commissioner of Patents, Washington, D.C. 20231, on this 15th day of October, 2002.

Anne M. Richards

Name

Signature